SEXUAL DYSFUNCTION

MCID provides new perspective on erectile function research

Maarten Albersen and Tom F. Lue

The erectile function domain of the International Index of Erectile Function score is a widely used patient-reported outcome metric and a frequent clinical trial end point. Rosen and colleagues determined minimal clinically important difference (MCID) values for this score to overcome discrepancies between statistical significance and clinical significance. Before these MCIDs are implemented in the clinic, urologists should be aware of the advantages and limitations of this instrument.

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For a study recently published in *European Urology*, Rosen and co-workers[1] tackled a major hurdle in optimization of the erectile function (EF) domain score of the International Index of Erectile Function (IIEF) questionnaire.[1] The IIEF-EF consists of six items pertaining to frequency, rigidity, penetration ability, and maintenance of erection, as well as confidence in erectile function.[2,3] Although the IIEF-EF domain score is widely employed as a clinical trial end point, there are currently no objective data on what constitutes a minimal clinically important difference (MCID) in this score. MCID was first defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management."[4] Later, this definition was simplified to "the smallest change that is important to patients", and MCID has been described as 'the new metric on the block' for patient-reported outcome studies.[5] Thus, the authors set out to estimate the MCID for the IIEF-EF domain.

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Data from 17 randomized, double-blind, placebo-controlled, parallel group clinical trials of the phosphodiesterase type 5 inhibitor tadalafil were pooled to generate a large population of patients ($n = 3,345$) treated for 12 weeks. An anchor-based approach was applied to determine the MCID for the IIEF-EF domain score[5] using an anchor consistent with the NIH definition of erectile dysfunction (ED), which is "the persistent inability to attain and maintain an erection sufficient for satisfactory sexual intercourse."[6] The external anchor was question seven of the IIEF, "Over the past 4 weeks, when you attempted sexual intercourse how often was it satisfactory for you?" Minimal improvement in the anchor from baseline to week 12 was arbitrarily defined as a change from 'little or no satisfactory intercourse' (score 1 or 2) to 'satisfactory intercourse sometimes' (score 3). 'No change' was defined as score 1 or 2 at baseline and score 1 or 2 at 12 weeks. Using these definitions, 1,240 men were identified with either minimal or no improvement, 863 of whom were used for development of the MCIDs, followed by subsequent validation in the remaining 377 patients.

A receiver operating characteristic (ROC)-based method was used to determine the final MCID, which was found to be 4 points. This value discriminated well between mean change in IIEF-EF scores of the placebo and active groups in the development sample. The estimated sensitivity and specificity were 0.74 and 0.73, respectively. MCIDs varied significantly according to severity of ED at baseline but did not differ between age group, geographic region, or ED etiology.

Using MCIDs in the analysis of patient-reported outcomes is a means of overcoming the discrepancy between clinically important significance and statistical significance. Statistically, a significant difference is one that is unlikely to be caused by chance and has a mathematical basis.[5] In health-related issues, however, a difference might be statistically significant but of little importance to the health status or quality of life of patients. In addition, the size of a tested sample will often contribute to statistical significance. Most multicenter clinical trials rely heavily on the sample size to show statistical significance while the treatment effect in itself might be relatively small. This has been the case for several clinical trials of ED treatment.

Rosen *et al.*[1] have now identified the difference in IIEF-EF score that might actually be meaningful from the patient's point of view. Any change greater than the MCID—in this case an increase of 4 in IIEF-EF score—can be considered meaningful. Any patient who reaches this threshold can thus be considered a responder to treatment. Logically, it follows that the ratio of responders to total patients who received a particular treatment indicates to a clinician the likelihood of their patients also responding favorably to the same treatment. This provides a new perspective on outcomes research in the field of ED. Previously, a

statistical significance was accepted as indicative of treatment benefit, but now one could claim that the statistically significant advantage of a treatment has to at least top the MCID to be of benefit from the patient's point of view.

> "MCID has been described as 'the new metric on the block' for patient-reported outcome studies"

However, there are some drawbacks to the development and use of MCIDs in ED research, of which clinicians should be aware before adopting this new metric in routine practice. Rosen and colleagues[1] investigated several of these limitations. First, different methods of determining MCIDs will result in different values, a point illustrated by the different MCIDs calculated using analysis of variance and ROC-based approaches in the discussed manuscript. Also, the resultant MCID will differ depending on the anchor. Although the anchor chosen by the authors was based on the NIH definition of ED, it might not be the ideal anchor for determining MCID, which is in essence a patient-perceived metric. Other anchors might be more relevant and could produce different MCID values. Second, contradictory to the initial definition of MCID, cost is not taken into account. For example, the patient might report improvement, but might consider the benefit not worth the cost. This is particularly applicable to ED research as phosphodiesterase 5 inhibitors are not covered by medical insurance in many countries and can be costly for patients, especially those undergoing long-term treatment, such as penile rehabilitation after radical prostatectomy. Third, changes are associated with baseline erectile function. This was beautifully illustrated by Rosen and colleagues,[1] who showed that the greater the severity of ED before treatment, the higher the MCID. This association with baseline severity can be explained by regression to the mean, and both floor and ceiling effects of patient-reported outcomes. The latter can be solved by proposing different MCIDs for different baseline scores, as illustrated in the manuscript. Last, clinicians should be cautious of adopting this metric to report worsening of erectile function. Whether a decrease of 4 points in the IIEF-EF domain score is indicative of a clinically meaningful worsening of erectile function was not validated.

Rosen and colleagues[1] should be congratulated for taking this important leap in patient-reported outcome research in erectile function and dysfunction. The newly defined MCID for erectile function outcome research using the IIEF-EF domain helps clinicians to discern between statistical and clinically significant differences. The MCID further helps to counsel patients on potential treatment benefit. Researchers and clinicians, however, should be aware of the limitations of such an instrument. Further research is needed to identify MCID values for other frequently employed patient-reported outcome measures such as the IIEF-5 and the sexual encounter profile. Furthermore, development and validation of an MCID for worsening of erectile functioning might be of benefit for counseling and evaluating patients with iatrogenic ED, which occurs following radical pelvic surgery and radiotherapy, or drug-induced ED.

*Laboratory of Experimental Urology, Department of Urology, University Hospitals Leuven, Herestraat 49m, Leuven BE-3000, Belgium (**M. Albersen**). University of California, 400 Parnassus Avenue, Suite A-610, San Francisco, CA 94143-0330, USA (**T. F. Lue**). Correspondence to: M. Albersen*
maarten.albersen@uzleuven.be

Competing interests
The authors declare no competing interests.

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INFECTION

Prostate biopsy—infection and prior fluoroquinolone exposure

Michael A. Liss

Prostate cancer screening has led to an increase in transrectal-ultrasonography (TRUS)-guided prostate biopsies. However, clinicians are becoming increasingly concerned that fluoroquinolone-resistant organisms are the cause of infectious complications in patients who have undergone this procedure. Two separate studies have shown that patients treated with fluoroquinolone prior to transrectal biopsy are at an increased risk of infectious complications.

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The transrectal approach for prostate biopsy was first described by Astraldi in 1937 and was expanded by Hodge and associates to incorporate transrectal ultrasonography in 1989.[1] Transrectal prostate biopsy is an outpatient procedure with a good safety record; therefore, an overall detection rate of only 30% has, thus far, been tolerated for this invasive diagnostic procedure.[2] However, this risk:benefit ratio changes as the risk of infectious complications increases. Such complications of prostate biopsy include urinary tract infection (UTI), epididymitis, orchitis, prostatitis, and sepsis—all usually attributable to *Escherichia coli*. The current incidence of any infectious complication following prostate biopsy is about 4%, with no definitive risk increase with the number of biopsy cores obtained or with repeat biopsies.[3,4] The likely mechanism of infection is introduction of bacteria from the rectum into the bladder, prostate and bloodstream during the biopsy. The American Urological Association (AUA) Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis and